HUMAN BRAIN DEVELOPMENT: WINDOWS OF OPPORTUNITY

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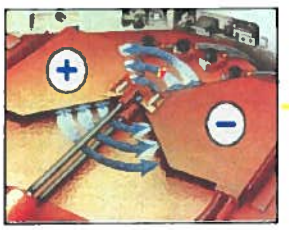
ADVANCES IN BRAIN IMAGING ALLOW AN UNPRECEDENTED OPPORTUNITY TO STUDY NORMAL AND ABNORMAL BRAIN DEVELOPMENT IN CHILDREN

- CT
- MRI
  - FUNCTIONAL MRI (fMRI)
  - DIFFUSION/PERFUSION MRI
  - DIFFUSION TENSOR IMAGING (DTI)
  - VOLUMETRIC MRI
- SPECT (cerebral blood flow)
- PET
  - GLUCOSE METABOLISM
  - $GABA_A$ (FLUMAZENIL)
  - SEROTONIN SYNTHESIS
  - PROTEIN SYNTHESIS
  - BRAIN INFLAMMATION

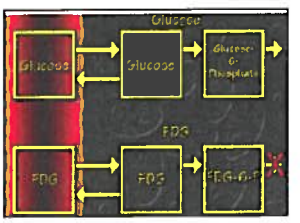
PET DATA ACQUISITION AND ANALYSIS



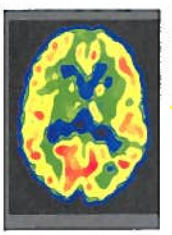
Proton acceleration

Isotope production

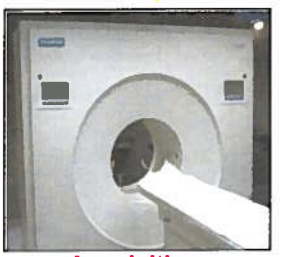
Labeling



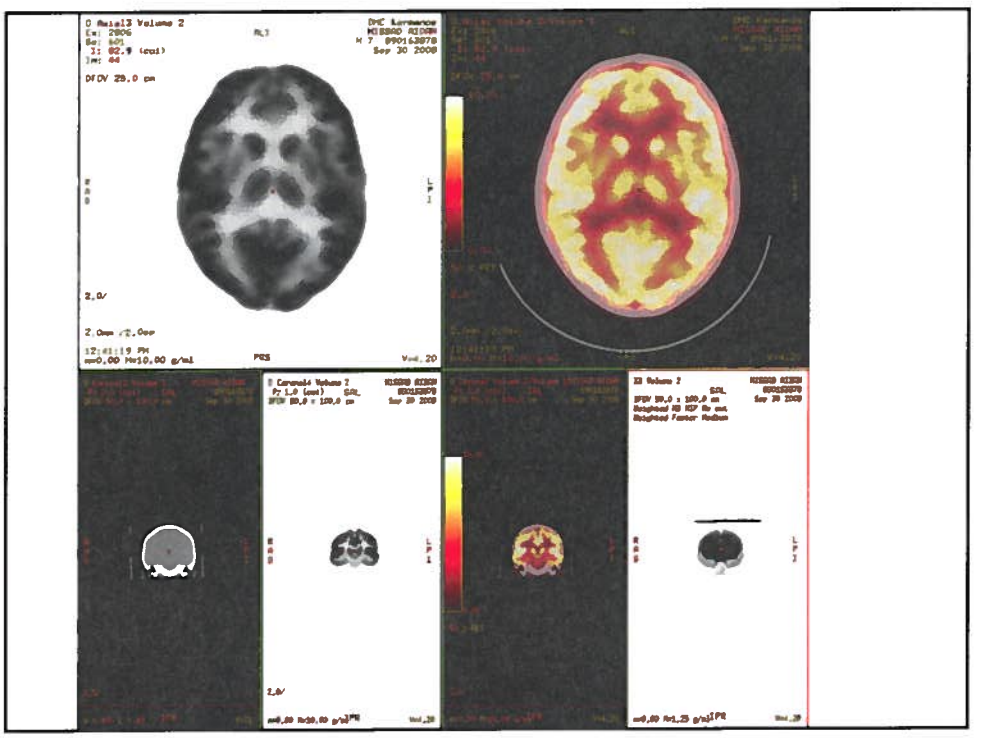
Modeling



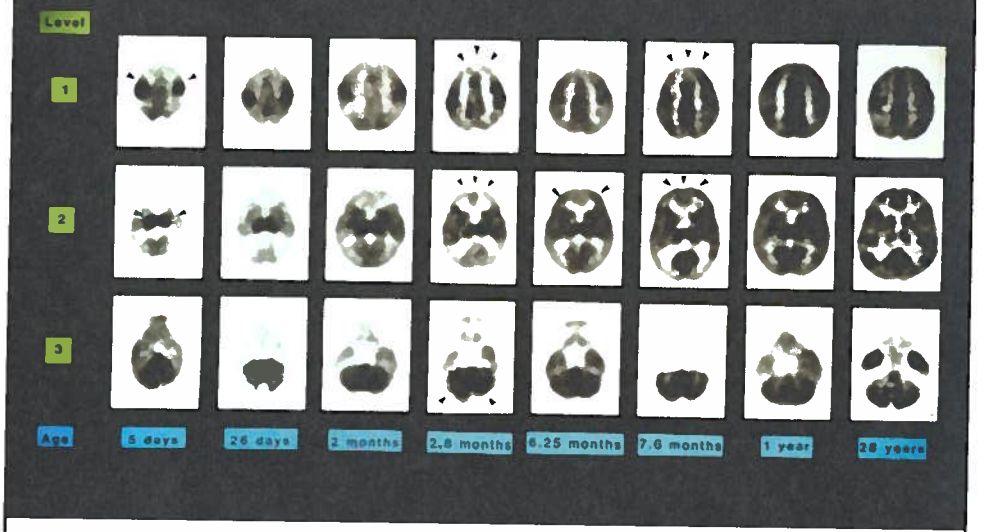
Imaging



Acquisition

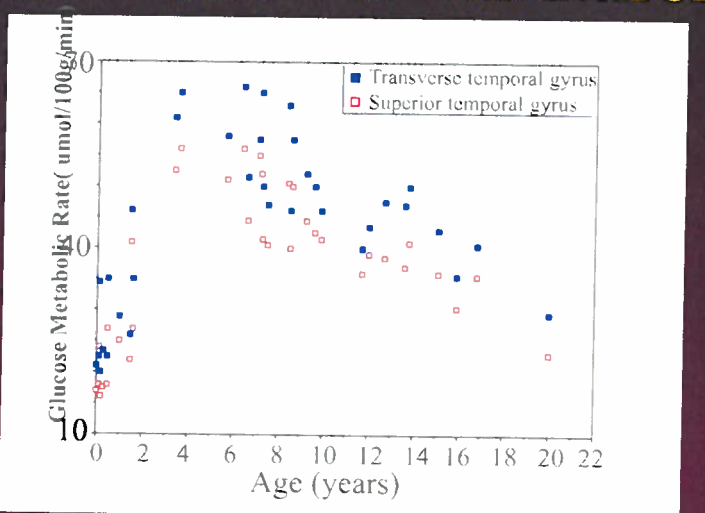


BRAIN GLUCOSE/ENERGY CONSUMPTION IN INFANCY

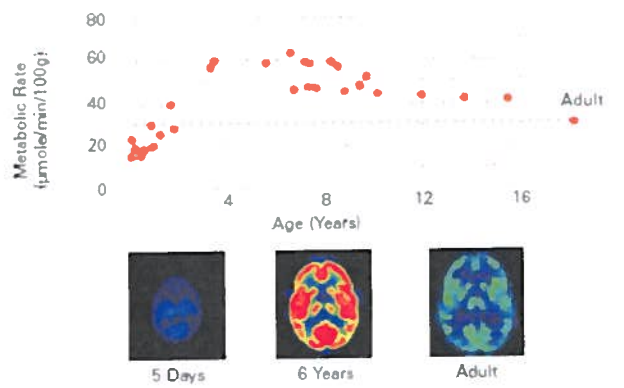


Chugani et al., 1987

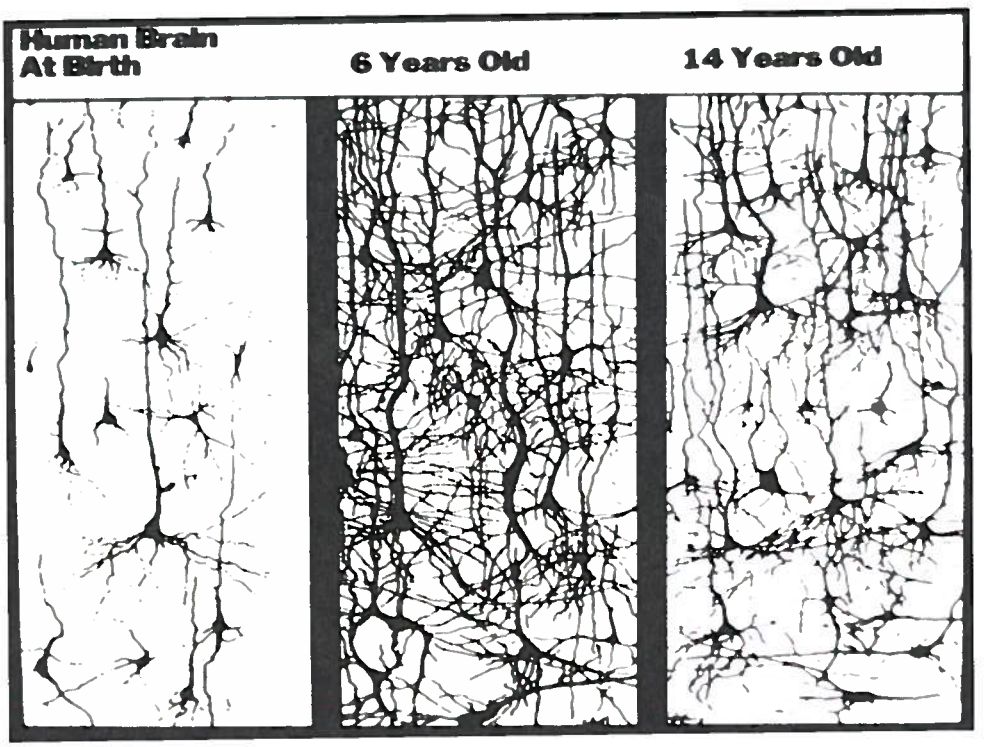
BRAIN GLUCOSE/ENERGY DEMAND IS HIGHER IN CHILDREN THAN IN ADULTS



The child's brain needs even more energy



Chugani, H.T., Neurodevelopmental Neuroimaging, New York 1996



DEVELOPMENTAL BRAIN PLASTICITY

- LANGUAGE AND SECOND LANGUAGE, DEAF SUBJECTS AND SIGN LANGUAGE, 'FERAL' CHILDREN: UPPER AGE OF ABOUT 10-14 YEARS
- LEFT TO RIGHT LANGUAGE TRANSFER POST LEFT HEMISPHERECTOMY: UPPER AGE OF 14 YRS
- STRING INSTRUMENT STUDY: UPPER AGE OF 14 YEARS
- VISUAL SYSTEM PLASTICITY: SHORT, < 2 YEARS
- EARLY IMPOVERISHMENT (MENTAL HEALTH): < 2 YEARS

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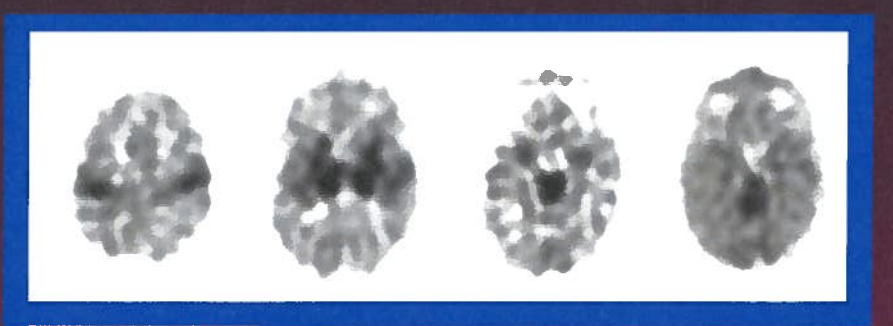
Neonatal Glucose Metabolism

Age 2 weeks



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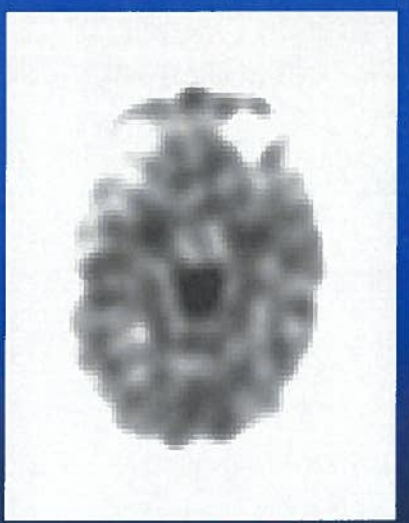
Neonatal Glucose Metabolism



ROMANIAN ORPHANS
Introduction

Impact of childhood social deprivation on brain function is largely unexamined

- **Socioeconomic problems in Romania in 1980's ----> over 65,000 children placed in orphanages (85% in first month of life)**
- **Child-caregiver ratios were 10:1 for infants and 20:1 for children over 3 years**
- **Infants spent up to 20 hours per day in their cribs unattended**

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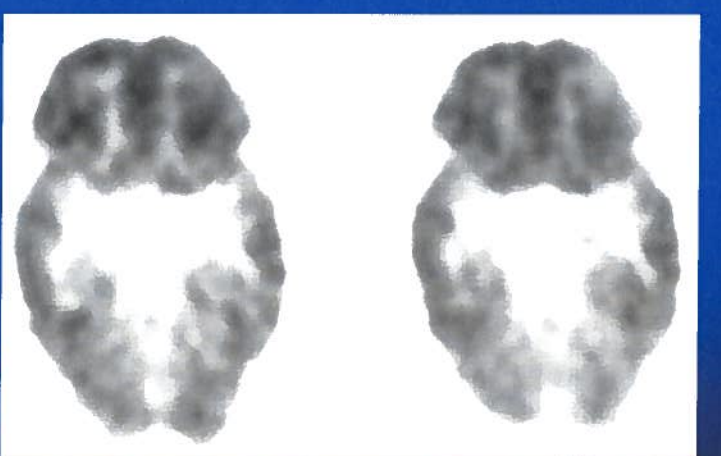
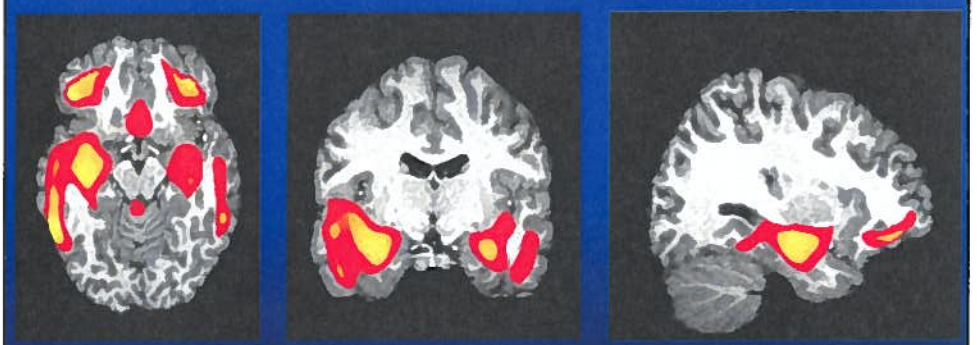
ROMANIAN ORPHANS: Follow-up

- At adoption, majority showed cognitive performance in mental retardation range (Rutter, 1998)
- Considerable recovery by age 4 years (Ames, 1997; Rutter, 1998), but deficits present at age 4 years persisted at age 6 years (O'Connor and Rutter, 2000)
- Behavioral abnormalities similar to some seen in socially deprived non-human primates (Suomi, 1997)
- Motor stereotypies, self-stimulatory behaviors, indiscrimantly friendly behavior, insecure attachment (Chisholm et al., 1995)

5 year old girl adopted from Kazakhstan



Statistical Parametric Mapping (SPM) Analysis on 10 Romanian Orphans: Areas of Decreased Glucose Metabolism



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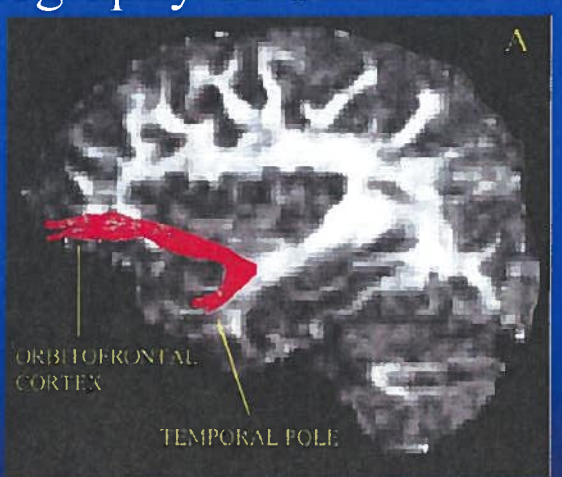
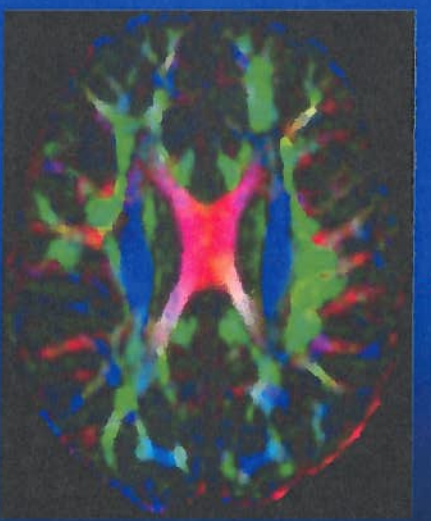
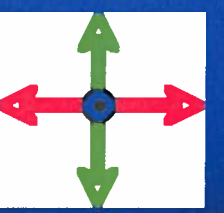
Tractography of Uncinate fasciculus



DTI: Direction Encoded Color Map



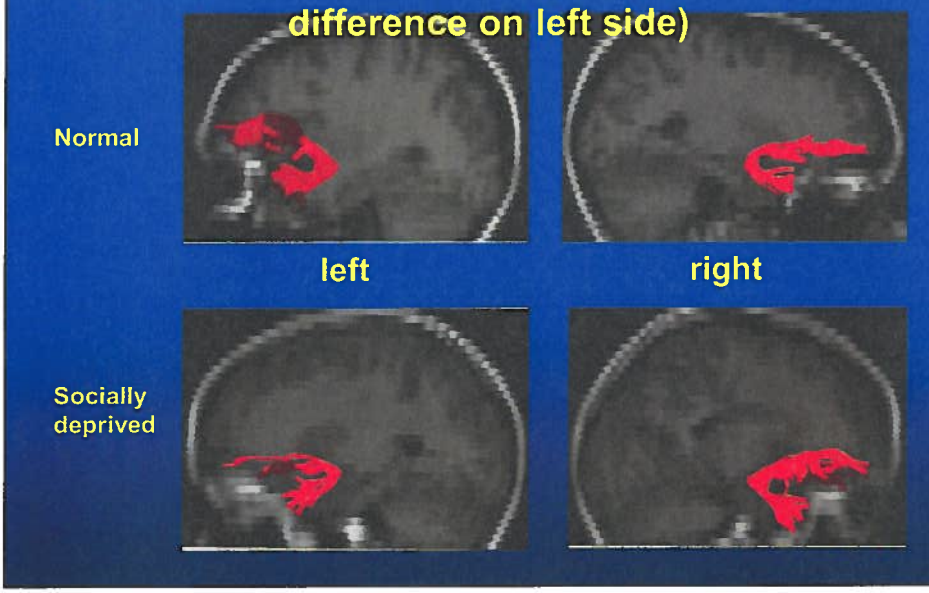


MAJOR TEMPORAL LOBE TRACTS AND CORTICOSPINAL TRACT

(A) UNCINATE FASCICULUS, (B) INFERIOR LONGITUDINAL FASCICULUS,
(C) ARCUATE FASCICULUS, (D) CORTICOSPINAL TRACT

DTI Fiber Tracking: Uncinate Fasciulus

Normal child vs. socially deprived child (marked difference on left side)



AUTISM

A developmental disorder characterized by problems in 3 domains:

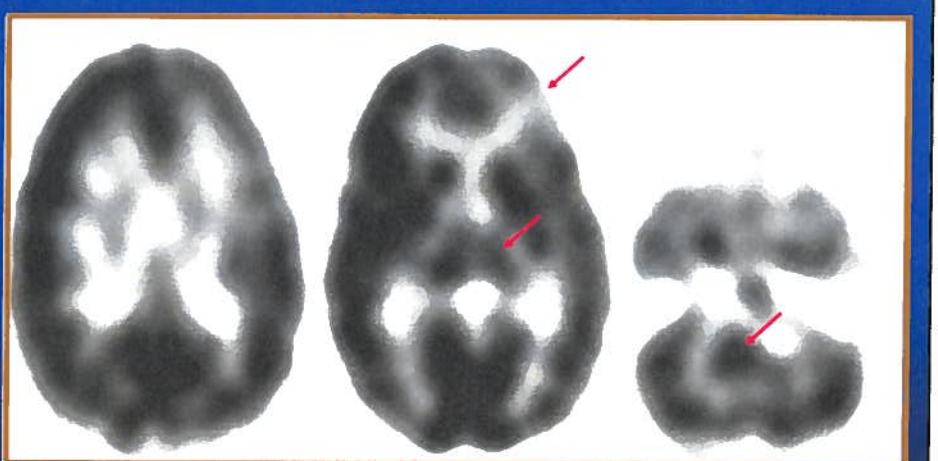
- COMMUNICATION
- SOCIAL INTERACTIONS
- STEREOTYPED BEHAVIORS

AUTISM

* IDIOPATHIC OR INFANTILE AUTISM: a genetic condition with 8% recurrence in siblings

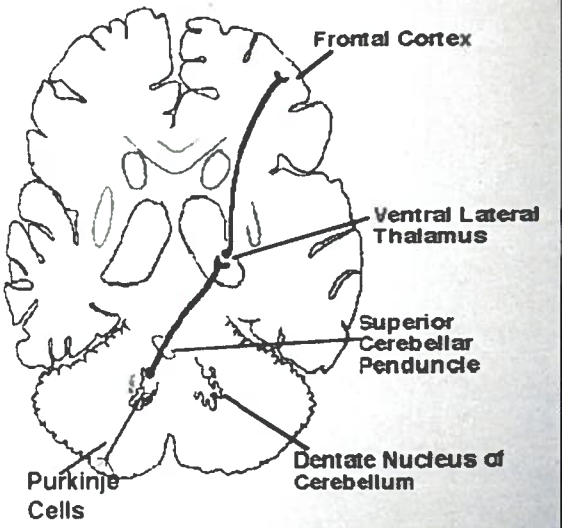
* SYMPTOMATIC/SYNDROMIC AUTISM:
- Congenital rubella
- Tuberous sclerosis complex
- Fragile-X syndrome
- Rett syndrome & other phenotypic expression of MECP2 mutations
- Angelman's syndrome, Down syndrome
- Celiac disease
- ARX gene mutations
- Various brain malformations

AUTISM: SEROTONIN PET SCANS



Diane Chugani et al., 1997

Alteration of Serotonin Synthesis in the Dentato-Thalamo-Cortical Pathway in Autism



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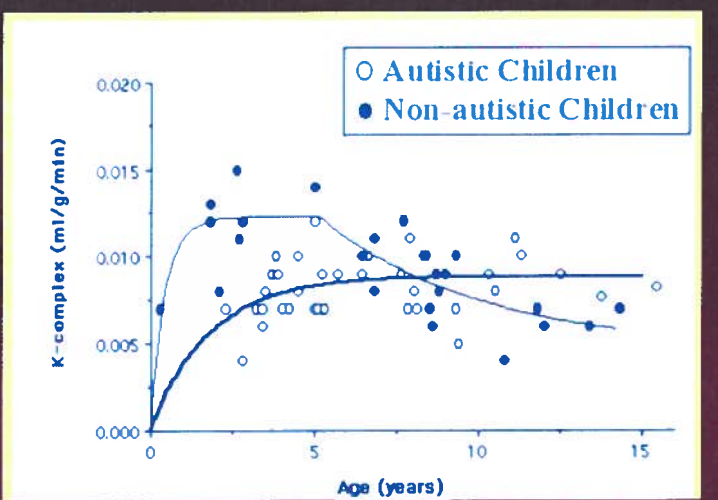
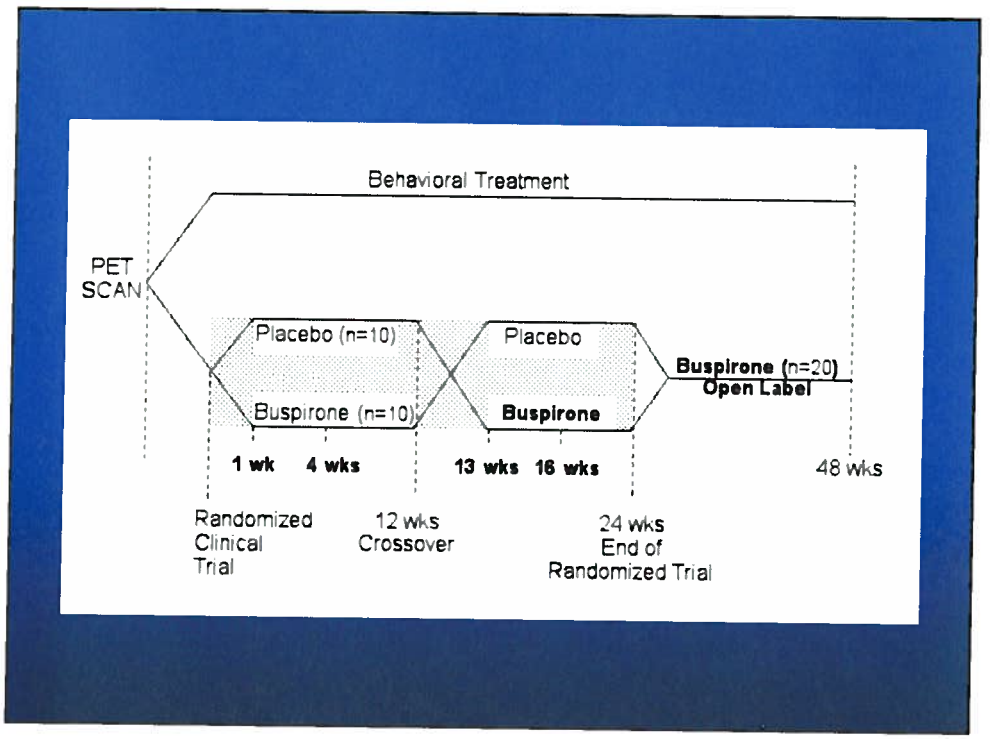
SEROTONIN SYNTHESIS : Autistic vs. non-autistic children



Diane Chugani et al., 1999



Improvement in two of three triad symptoms:

1. **Social interaction in younger children**, as rated by parents (p=.027, Figure 2) *and* examiners (p=.029, Figure 3) was improved with drug.
2. **Repetitive behavior in younger children**, as rated by parents, (p=.017) was improved.
   - Specifically, **parent-reported mental rigidity in younger children** was improved with drug (p=.007)

Improvement in associated symptoms:

1. **Parent-reported sensory problems in younger children** improved with drug (p=.025)
   - Sensory seeking improved across age groups (p=.014), but more so more in younger children, with drug (p=.047)
2. **Examiner-rated anxiety** improved with drug across age groups, (p=.010)

•Treatment with buspirone was associated with improvements in two of three triad symptoms, social interaction and repetitive/stereotyped behavior, as well as sensory problems and anxiety.

• Gains were greater for younger children, and associated with pretreatment serotonin synthesis capacity (K-complex values).

•Greater responsiveness in the younger children may reflect greater plasticity and susceptibility for change in the long term developmental course in the serotonin system involved in the expression of autism.

CONCLUSION (1)

- NORMAL BRAIN MATURATION AND VARIOUS DEVELOPMENTAL DISORDERS, SUCH AS AUTISM, CAN BE STUDIED WITH NEW IMAGING METHODS.
- IN NORMAL CHILDREN, THERE ARE 'WINDOWS OF OPPORTUNITY' OR 'CRITICAL PERIODS' UP TO ADOLESCENCE (NOT JUST 0-3) DURING WHICH CERTAIN SKILLS (e.g., 2nd LANGUAGE) CAN BE ACQUIRED WITH GREATER EASE THAN LATER IN LIFE.
- CHILDREN WHO ARE 'ENVIRONMENTALLY IMPOVERISHED' TYPICALLY MISS MUCH OF THIS 'WINDOW OF OPPORTUNITY' AND MANY POSITIVE GENETIC TRAITS ARE NOT REALIZED BECAUSE OF LACK OF ENVIRONMENTAL EXPOSURE

CONCLUSION (2)

- SOME 'CRITICAL PERIODS' ARE SHORT, e.g., EARLY SOCIAL INTERACTIONS, THE DEPRIVATION OF WHICH CAN LEAD TO ATTACHMENT DIFFICULTIES AND PSYCHOPATHOLOGY. A NEGATIVE ENVIRONMENT WILL STRENGTHEN THE EXPRESSION OF NEGATIVE GENETIC BEHAVIORAL TRAITS.
- AUTISTIC CHILDREN ALSO HAVE 'WINDOWS OF OPPORTUNITY' DURING WHICH AGGRESSIVE TREATMENT WILL LEAD TO MILDER DISORDER WITH IMPROVED QUALITY OF LIFE AND LESSEN THE BURDEN FOR FUTURE RESOURCES. THIS CAN TRANSLATE INTO AN ENORMOUS ECONOMIC SAVING.
- INVESTMENTS WHICH PROVIDE A RICH AND SUPPORTIVE FAMILY ENVIRONMENT FOR INFANTS AND CHILDREN MAKE GOOD BIOLOGICAL SENSE, AND WILL INCREASE THEIR CHANCES OF ACHIEVING THEIR FULL GENETIC POTENTIAL.
- CHILDREN WHO ARE EXPOSED TO A STABLE AND ENRICHED ENVIRONMENT WILL ALSO GROW UP TO BE CREATIVE INDIVIDUALS WHO WILL STRENGTHEN THE WORK FORCE AND IMPROVE THE ECONOMY.

HOW TO INVEST IN OUR CHILDREN? A WISH LIST

- ACCESS OF FREE ENRICHMENT PROGRAMS TO NORMAL CHILDREN FROM FIRST YEAR OF LIFE. MONITOR FOR QUALITY. CREATES JOBS!
- EMPHASIS ON HEALTH BENEFITS, NOT BUDGET CUTS IN THIS AREA!
- PASSAGE OF AUTISM INSURANCE LEGISLATION TO COVER INTENSIVE EARLY INTERVENTION. JOBS!!
- FREE SUMMER ENRICHMENT PROGRAMS FOR THOSE WHO QUALIFY BASED ON INCOME. JOBS!!
- FOCUS: PROBLEM SOLVING SKILLS AND CREATIVITY
- EARLY SECOND LANGUAGE (various languages)
- TRACK THESE CHILDREN AND COMPARE TO HISTORICAL CONTROLS AND TO OTHER STATES